Endocrinization of FGF1 produces a neomorphic and potent insulin sensitizer.

Journal: Nature

Publication Year: 2014

Authors: Jae Myoung Suh, Johan W Jonker, Maryam Ahmadian, Regina Goetz, Denise Lackey, Olivia Osborn, Zhifeng Huang, Weilin Liu, Eiji Yoshihara, Theo H van Dijk, Rick Havinga, Weiwei Fan, Yun-Qiang Yin, Ruth T Yu, Christopher Liddle, Annette R Atkins, Jerrold M Olefsky, Moosa Mohammadi, Michael Downes, Ronald M Evans

PubMed link: 25043058

Funding Grants: Metabolically-driven epigenetic changes in iPSC reprogramming

Public Summary:
Fibroblast growth factor 1 (FGF1) is an autocrine/paracrine regulator whose binding to heparan sulphate proteoglycans effectively precludes its circulation1,2.AlthoughFGF1isknownasamitogenicfactor, FGF1 knockout mice develop insulin resistance when stressed by a high-fat diet, suggesting a potential role in nutrient homeostasis3,4. Here we show that parenteral delivery of a single dose of recombinant FGF1(rFGF1) results in potent, insulin-dependent lowering of glucose levels indiabeticmice that is dose-dependent but doesnot lead to hypoglycaemia. Chronic pharmacological treatment with rFGF1 increases insulin-dependent glucose uptake in skeletal muscle and suppresses the hepatic production of glucose to achieve whole-body insulin sensitization.The sustained glucose lowering and insulin sensitization attributed to rFGF1 are not accompanied by the side effects of weight gain, liver steatosis and bone loss associated with current insulin-sensitizingtherapies.We also showthat the glucose-lowering activity of FGF1 can be dissociated fromits mitogenic activity and is mediated predominantly viaFGF receptor 1 signalling.Thus wehave uncovered an unexpected, neomorphic insulin-sensitizing action for exogenous non-mitogenic human FGF1 with therapeutic potential for the treatment of insulin resistance and type 2 diabetes.

Scientific Abstract:
Fibroblast growth factor 1 (FGF1) is an autocrine/paracrine regulator whose binding to heparan sulphate proteoglycans effectively precludes its circulation. Although FGF1 is known as a mitogenic factor, FGF1 knockout mice develop insulin resistance when stressed by a high-fat diet, suggesting a potential role in nutrient homeostasis. Here we show that parenteral delivery of a single dose of recombinant FGF1 (rFGF1) results in potent, insulin-dependent lowering of glucose levels in diabetic mice that is dose-dependent but does not lead to hypoglycaemia. Chronic pharmacological treatment with rFGF1 increases insulin-dependent glucose uptake in skeletal muscle and suppresses the hepatic production of glucose to achieve whole-body insulin sensitization. The sustained glucose lowering and insulin sensitization attributed to rFGF1 are not accompanied by the side effects of weight gain, liver steatosis and bone loss associated with current insulin-sensitizing therapies. We also show that the glucose-lowering activity of FGF1 can be dissociated from its mitogenic activity and is mediated predominantly via FGF receptor 1 signalling. Thus we have uncovered an unexpected, neomorphic insulin-sensitizing action for exogenous non-mitogenic human FGF1 with therapeutic potential for the treatment of insulin resistance and type 2 diabetes.

Source URL: https://www.cirm.ca.gov/about-cirm/publications/endocrinization-fgf1-produces-neomorphic-and-potent-insulin-sensitizer